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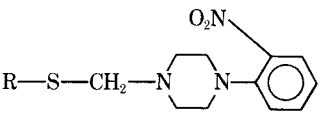
Synthesis and *In Vitro* Antimicrobial Evaluation of Hydrazones of 1-Phenyl-, 1-Benzyl-, and 1-Benzhydryl-4-aminopiperazines

D. K. YUNG, D. E. MAHONY, and L. W. WHITEHOUSE

Abstract □ Thirty new hydrazones of 1-phenyl-, 1-benzyl-, and 1-benzhydryl-4-aminopiperazines were prepared and tested for *in vitro* antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Clostridium perfringens*, and *Mycobacterium phlei*, and for antifungal activity against *Saccharomyces cerevisiae* and *Candida albicans*. Activities were detected in seven compounds. A bactericidal action against *B. subtilis* and *Cl. perfringens* was noted in 1-phenyl-4-(5-nitro-2-furfurylideneamino)piperazine. 1-Benzyl-4-(5-nitro-2-furfurylideneamino)piperazine and 1-benzhydryl-4-(5-nitro-2-furfurylideneamino)piperazine were found to suppress the growth of *B. subtilis*. 1-Benzhydryl-4-isonicotinylideneaminopiperazine showed a broad spectrum of activity, inhibiting the growth of *M. phlei*, *S. aureus*, *B. subtilis*, and *S. cerevisiae*. 1-Benzhydryl-4-nicotinylideneaminopiperazine had a bacteriostatic effect on *M. phlei*, while 1-benzyl-4-[4-(4-methoxyphenyl)-3-butene-2-ylideneamino]piperazine exhibited a bactericidal action against the same bacteria. A bacteriostatic effect on *S. aureus* was observed in 1-benzyl-4-(5-nitro-2-hydroxybenzylideneamino)piperazine. None of the hydrazones showed antimicrobial activity against *E. coli*, *P. aeruginosa*, and *C. albicans*.

Keyphrases □ Hydrazones of 1-phenyl-, 1-benzyl-, and 1-benzhydryl-4-aminopiperazines—synthesis □ Antimicrobial activity—hydrazones □ Structure-activity relationships—hydrazones □ IR spectrophotometry—structure

Numerous piperazine derivatives have been reported in the literature to have antibacterial activity. For example, Nakanishi and Muro (1) noted that the unsymmetrically 1,4-disubstituted piperazines (I) were



R = 4-ClC_6H_4, CH_3CH_2, $C_6H_5CH_2$, 4-$CH_3OC_6H_4$, or 4-$CH_3C_6H_4$

I

useful bactericides and fungicides. Pedrazzoli and Dall'-Asta (2) synthesized 1-[2-(2,4-dichlorobenzoyloxy)-2-(3,4-dichlorophenyl)ethyl]-4-methylpiperazine and a number of other related 1-phenethyl-4-methylpiperazine derivatives, and they reported that these compounds exhibited both trichomonicide and amebicide activities. Hydrazones containing the piperazine nucleus have recently been examined as potential antimicrobial agents. Kozhukharov and Kharizanova (3) reported that the diisonicotinyl hydrazone of 1,4-bis(benzoylethyl)piperazine showed tuberculostatic activity. Recent work by Prescott *et al.* (4) indicated that the bishydrazones obtained by reacting 1,4-diaminopiperazine with salicylaldehyde, 5-nitrosalicylaldehyde, and 3,4-dichlorobenzaldehyde showed a high *in vitro* antibacterial activity against *Staphylococcus aureus*.

As part of a continuous investigation on piperazine compounds with potential medicinal uses, series of hydrazones of 1-phenyl-, 1-benzyl-, and 1-benzhydryl-4-aminopiperazines were prepared and their *in vitro* antibacterial and antifungal activities were determined. Eight aldehydes, 2-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, 4-diethylaminobenzaldehyde, 5-nitro-2-hydroxybenzaldehyde, 3,4-dichlorobenzaldehyde, 5-nitro-2-furfural, isonicotinaldehyde, and nicotinaldehyde, and three ketones, 4-methoxypropiophenone, 4-(2-hydroxyphenyl)-3-buten-2-one, and 4-(4-methoxyphenyl)-3-buten-2-one, were used in the formation of the hydrazones.

EXPERIMENTAL[1]

Chemical Synthesis—All melting points were determined using a Thomas-Hoover Unimelt apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer model 237B spectrophotometer and were in agreement with the assigned structures.

With the exception of 5-nitro-2-furfural, all aldehydes and ketones used in this work were obtained from commercial sources. 5-Nitro-2-furfural was prepared according to the procedure reported by Kochergin and Karpov (5).

The preparation of the title compounds consisted of monosubstitution of piperazine, nitrosation of the monosubstituted piperazines, reduction of the nitroso group, and condensation of the aldehydes or ketones with the 1-substituted-4-aminopiperazines.

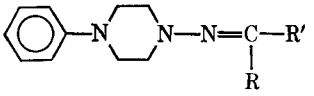
1-Benzylpiperazine and 1-benzhydrylpiperazine were prepared according to the method of Kitchen and Pollard (6). 1-Phenylpiperazine was obtained commercially.

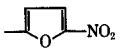
Nitrosation of 1-phenyl-, 1-benzyl-, and 1-benzhydrylpiperazines and subsequent reduction to 4-aminopiperazines were carried out by the methods described in the literature (7–10).

Formation of Hydrazones—A solution of the 1-substituted-4-aminopiperazine (0.0125 mole) in ethanol was treated with the appropriate aldehyde or ketone (0.0125 mole) dissolved in the same solvent. If no hydrazone was formed immediately, the reaction

[1] Elemental analyses were performed by Strauss Microanalytical Laboratory, Oxford, England.

Table I—Hydrazones of 1-Phenyl-4-aminopiperazine



Compound Number	R	R′	Yield, %	M.p.	Recrystallization Solvent	Formula	Analysis, % Calcd.	Found
1	H	2-HOC_6H_4	74	139.5–141.5°	EtOH	$C_{17}H_{19}N_3O$	C, 72.57 H, 6.81 N, 14.93	C, 72.59 H, 7.02 N, 14.61
2	H	3-HOC_6H_4	34	195–197°	EtOH	$C_{17}H_{19}N_3O$	C, 72.57 H, 6.81 N, 14.93	C, 72.68 H, 6.87 N, 14.54
3	H	4-$(C_2H_5)_2NC_6H_4$	76	192.5–193.5°	EtOH–$CHCl_3$	$C_{21}H_{28}N_4$	C, 74.96 H, 8.39 N, 16.65	C, 75.15 H, 8.17 N, 17.02
4	H	5-NO_2-2-HOC_6H_3	98	223–225°	—[a]	$C_{17}H_{18}N_4O_3$	C, 62.57 H, 5.56 N, 17.17	C, 62.92 H, 5.78 N, 17.08
5	H	3,4-$Cl_2C_6H_3$	93	176–177.5°	Me_2CO	$C_{17}H_{17}Cl_2N_3$	C, 61.09 H, 5.13 N, 12.57	C, 60.76 H, 4.68 N, 12.98
6	H		40	152–154°	EtOH–Me_2CO	$C_{15}H_{16}N_4O_3$	C, 59.99 H, 5.37 N, 18.66	C, 60.35 H, 5.37 N, 18.62
7	H		98	163–164.5°	EtOH	$C_{16}H_{18}N_4$	C, 72.15 H, 6.81 N, 21.04	C, 72.19 H, 6.81 N, 20.82
8	H		72	116.5–118.5°	EtOH–H_2O	$C_{16}H_{18}N_4$	C, 72.15 H, 6.81 N, 21.04	C, 72.22 H, 6.86 N, 20.86
9	C_2H_5	4-$CH_3OC_6H_4$	18	140–142°	EtOH–H_2O	$C_{20}H_{25}N_3O$	C, 74.27 H, 7.79 N, 12.99	C, 74.09 H, 7.89 N, 12.95
10	CH_3	2-$HOC_6H_4CH{=}CH$	40	181–182°	EtOH–H_2O	$C_{20}H_{23}N_3O$	C, 74.74 H, 7.21 N, 13.07	C, 74.63 H, 6.55 N, 12.84
11	CH_3	4-$CH_3OC_6H_4CH{=}CH$	38	179–181°	EtOH	$C_{21}H_{25}N_3O$	C, 75.19 H, 7.51 N, 12.53	C, 75.35 H, 7.57 N, 12.68

[a] Washed with acetone.

mixture was refluxed for 1 hr. and cooled. The product was collected and recrystallized from a suitable solvent.

Solvents for recrystallization and physical data for the hydrazones are listed in Tables I–III.

Microbiological Evaluation—Representative members of six genera of bacteria and two genera of fungi were used in the screening of the new hydrazones for antimicrobial activity.[2] The six bacterial genera were represented by two Gram-positive bacteria, *S. aureus* and *Bacillus subtilis*, two Gram-negative bacteria, *Escherichia coli* and *Pseudomonas aeruginosa*, one acid-fast bacterium, *Mycobacterium phlei*, and one anaerobic Gram-positive bacterium, *Clostridium perfringens*. The two fungi were *Saccharomyces cerevisiae* and *Candida albicans*. With the exception of *Cl. perfringens*, the bacteria were grown at 37° for 18 hr. and maintained thereafter at 4° on brain-heart infusion agar slopes[3]. *Cl. perfringens* was grown and maintained under similar conditions in cooked meat medium.[4] The fungi were similarly treated, but grown on slopes of Sabouraud's dextrose agar.[3] Subcultures were made from these stock cultures when necessary.

Preparation of Microorganisms for Evaluation—S. aureus, B. subtilis, E. coli, and *P. aeruginosa* were subcultured from the stock cultures to brain-heart infusion slopes and these were incubated at 37° for 18–20 hr. The bacterial growth was then washed from these slopes with brain-heart infusion broth (1 ml., Difco). This suspension of organisms was diluted 1:1000 with the same broth to provide a count of 1×10^6 to 1×10^7 viable organisms/milliliter.

Cl. perfringens was subcultured into cooked meat medium and incubated in a water bath for 18–20 hr. at 37°. This subculture (1 ml.) was then transferred to brain-heart infusion broth (10 ml.) containing sodium thioglycollate (0.1% w/v), which had been previously boiled to drive off dissolved oxygen from the medium. This broth culture was incubated in a water bath at 37° for 3 hr. and diluted 1:1000 in similar broth.

In the case of *M. phlei*, transfer was made from the stock culture to a sterile conical flask containing brain-heart infusion broth (20 ml.) and an aqueous solution of polysorbate 80[5] (10% w/v, 0.01 ml.). The flask was incubated at 37° for 3 days on a shaker. A dilution of 1:1000 was made at the end of the incubation period in similar broth.

The two cultures of fungi were prepared by inoculating Sabouraud's dextrose broth (20 ml.) with the organisms from the stock cultures. The subcultures after the incubation period of 18–20 hr. at 37° were diluted 1:1000 with the same broth.

Determination of Antimicrobial Activity—The test compounds in acetone were screened for antimicrobial activity at a concentration of 30 mcg./ml. Hydrazones that exhibited activity at this level were studied further to determine their minimum inhibitory concentrations (MIC) by an *in vitro* serial twofold dilution procedure. Broth cultures containing no compound were incorporated as positive controls. After each MIC determination, a loopful of solution from each dilution tube showing complete inhibition of bacterial growth was streaked out on brain-heart infusion agar plates, or on Sabouraud's dextrose agar plates in the case of *S. cerevisiae*, to determine whether the action of the compound was bactericidal or bacteriostatic in nature. The results are listed in Table IV.

RESULTS AND DISCUSSION

The hydrazones synthesized in this work were found to be insoluble in water and, in spite of the basic piperazine nucleus, they were only slightly soluble in 5 *N* HCl. A search of the literature (11, 12) revealed that ethanol and acetone had been used as solvents in screening potential antibacterial compounds. Since the hydrazone

[2] These microorganisms were obtained from the Department of Microbiology, Dalhousie University, Halifax, Nova Scotia, Canada.
[3] Baltimore Biological Laboratories, Baltimore, Md.
[4] Difco Laboratories, Detroit, Mich.
[5] Tween 80.

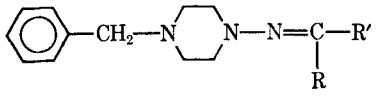


Table II—Hydrazones of 1-Benzyl-4-aminopiperazine

Compound Number	R	R′	Yield, %	M.p.	Recrystallization Solvent	Formula	Analysis, % Calcd.	Found
12	H	2-HOC_6H_4	77	135–136.5°	EtOH	$C_{18}H_{21}N_3O$	C, 73.19 H, 7.17 N, 14.23	C, 73.48 H, 7.09 N, 14.01
13	H	3-HOC_6H_4	80	179–181°	EtOH	$C_{18}H_{21}N_3O$	C, 73.19 H, 7.17 N, 14.23	C, 73.30 H, 6.89 N, 13.90
14	H	4-$(C_2H_5)_2NC_6H_4$	75	78.5–80°	EtOH–H_2O	$C_{22}H_{30}N_4$	C, 75.39 H, 8.63 N, 15.99	C, 75.67 H, 8.59 N, 15.88
15	H	5-NO_2,2-HOC_6H_3	67	159–160°	EtOH–Me_2CO	$C_{18}H_{20}N_4O_3$	C, 63.52 H, 5.92 N, 16.46	C, 63.54 H, 5.96 N, 15.70
16	H	3,4-$Cl_2C_6H_3$	75	83–85°	EtOH	$C_{18}H_{19}Cl_2N_3$	C, 62.08 H, 5.50 N, 12.07	C, 62.23 H, 5.52 N, 12.34
17	H		49	96.5–98°	EtOH	$C_{16}H_{18}N_4O_3$	C, 61.14 H, 5.77 N, 17.82	C, 61.12 H, 5.96 N, 17.59
18	H		63	95–98°	EtOH–H_2O	$C_{17}H_{20}N_4$	C, 72.83 H, 7.19 N, 19.98	C, 73.28 H, 7.14 N, 19.78
19	H		64	104.5–106°	EtOH–H_2O	$C_{17}H_{20}N_4$	C, 72.83 H, 7.19 N, 19.98	C, 72.85 H, 6.96 N, 19.85
20	C_2H_5	4-$CH_3OC_6H_4$	98	68–70°	Me_2CO	$C_{21}H_{27}N_3O$	C, 74.74 H, 8.07 N, 12.45	C, 74.79 H, 8.11 N, 12.30
21	CH_3	2-HO—C_6H_4CH=CH	51	145–147°	—[a]	$C_{21}H_{25}N_3O$	C, 75.19 H, 7.51 N, 12.53	C, 74.94 H, 7.36 N, 12.38
22	CH_3	4-$CH_3OC_6H_4$CH=CH	33	103.5–104.5°	EtOH–H_2O	$C_{22}H_{27}N_3O$	C, 75.61 H, 7.79 N, 12.02	C, 75.80 H, 7.89 N, 11.84

[a] Washed with petroleum ether.

compounds dissolved readily in acetone, all microbiological evaluations were carried out in this solvent. In a series of experiments designed to study the effect of acetone on the growth of *S. aureus*, *B. subtilis*, and *E. coli*, acetone did not have the ability to inhibit the growth of these bacteria below 12.5% v/v. The acetone content of all the test solutions was very much below this concentration. For this reason, it was assumed that any activity observed in the testings was due to the compound tested and not to the solvent itself.

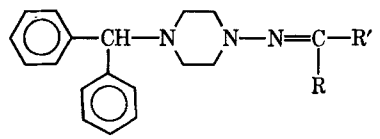


Table III—Hydrazones of 1-Benzhydryl-4-aminopiperazine

Compound Number	R	R′	Yield, %	M.p.	Recrystallization Solvent	Formula	Analysis, % Calcd.	Found
23	H	2-HOC_6H_4	50	165–166°	EtOH–Me_2CO	$C_{24}H_{25}N_3O$	C, 77.60 H, 6.78 N, 11.31	C, 77.48 H, 6.76 N, 11.41
24	H	4-$(C_2H_5)_2NC_6H_4$	42	123–124°	EtOH	$C_{28}H_{34}N_4$	C, 78.83 H, 8.03 N, 13.13	C, 79.11 H, 8.00 N, 13.26
25	H	5-NO_2,2-HOC_6H_3	64	193.5–195°	Me_2CO	$C_{24}H_{24}N_4O_3$	C, 69.21 H, 5.81 N, 13.45	C, 69.43 H, 5.81 N, 13.18
26	H	3,4-$Cl_2C_6H_3$	67	135.5–136.5°	EtOH–Me_2CO	$C_{24}H_{23}Cl_2N_3$	C, 67.93 H, 5.46 N, 9.90	C, 68.20 H, 5.43 N, 9.69
27	H		50	147–148°	EtOH	$C_{22}H_{22}N_4O_3$	C, 67.68 H, 5.68 N, 14.35	C, 67.42 H, 5.62 N, 14.29
28	H		73	122–124°	EtOH–H_2O	$C_{23}H_{24}N_4$	C, 77.50 H, 6.79 N, 15.72	C, 77.43 H, 6.77 N, 15.65
29	H		82	128.5–130.5°	EtOH–H_2O	$C_{23}H_{24}N_4$	C, 77.50 H, 6.77 N, 15.72	C, 77.35 H, 6.52 N, 15.63
30	CH_3	4-$CH_3OC_6H_4$CH=CH	52	175–177°	EtOH–Me_2CO	$C_{28}H_{31}N_3O$	C, 79.02 H, 7.34 N, 9.87	C, 78.91 H, 6.94 N, 9.88

Table IV—Approximate MIC (mcg./ml.) of Some Hydrazones

Compound Number	Compound	*S. aureus*[a]	*B. subtilis*[a]	*Cl. perfringens*[b]	*M. phlei*[c]	*S. cerevisiae*[a]
6	1-Phenyl-4-(5-nitro-2-furfurylidene-amino)piperazine	—[d]	1.56[g]	15[g]	—	—
15	1-Benzyl-4-(5-nitro-2-hydroxybenzyl-ideneamino)piperazine	25[e,f]	—	—	—	—
17	1-Benzyl-4-(5-nitro-2-furfurylidene-amino)piperazine	—	6.25[g,h]	—	—	—
22	1-Benzyl-4-[4-(4-methoxyphenyl)-3-butene-2-ylideneamino]piperazine	—	—	—	15[f]	—
27	1-Benzhydryl-4-(5-nitro-2-furfuryl-ideneamino)piperazine	—	0.78[g]	15[g,i]	—	—
28	1-Benzhydryl-4-isonicotinylidene-aminopiperazine	6.25[f]	6.25[f]	—	30[f,j]	15[k]
29	1-Benzhydryl-4-nicotinylideneamino-piperazine	—	—	—	30[f,j]	—

[a] Determined after 18–20 hr. of incubation at 37°. [b] Determined after 16–18 hr. of incubation at 37° under anaerobic conditions. [c] Determined after 48 hr. of incubation at 37°. [d] No inhibition of growth at 30 mcg./ml. [e] Partial inhibition at 12.5, 6.25, and 3.13 mcg./ml. [f] Bacteriostatic at MIC. [g] Bactericidal at MIC. [h] Partial inhibition at 3.13 and 1.56 mcg./ml. [i] Partial inhibition at 7.5, 3.8, and 1.9 mcg./ml. [j] Partial inhibition at 15 mcg./ml. [k] Fungistatic at MIC.

The new compounds were screened for the antimicrobial activity against six genera of bacteria and two genera of fungi, as listed in the *Experimental* section, at a concentration of 30 mcg./ml. It was believed that any significant activity should be detected at this level. Results of the screening indicated that *S. aureus* was susceptible to Compounds 15 and 28; *B. subtilis* to Compounds 6, 17, 27, and 28; *Cl. perfringens* to Compounds 6 and 27; and *M. phlei* to Compounds 22, 28, and 29. The Gram-negative *E. coli* and *P. aeruginosa* were not sensitive to any hydrazone. Only Compound 29 showed antifungal activity against *S. cerevisiae*. Not one hydrazone was active against *C. albicans*.

On the basis of the results of the microbiological assays, it was not possible to correlate clearly the structure of the hydrazones with the antimicrobial activity. However, a few observations were rather obvious.

1. The hydrazones of 1-phenyl-, 1-benzyl-, and 1-benzhydryl-4-aminopiperazines derived from ketones [for example, 4-methoxypropriophenone and 1-(2-hydroxyphenyl)-3-buten-2-one] and from substituted benzaldehydes (for example, 2-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, 4-diethylaminobenzaldehyde, and 3,4-dichlorobenzaldehyde) did not show any *in vitro* antibacterial or antifungal activity. However, the hydrazones prepared from the heterocyclic aldehydes (for example, 5-nitro-2-furfural, isonicotinaldehyde, and nicotinaldehyde) were more promising as potential antimicrobial agents.

2. Of the four hydrazones that showed antibacterial activity against *B. subtilis*, three were 5-nitrofuran derivatives. Compound 27 was the most active, having a MIC value of 0.78 mcg./ml. Replacing the 5-nitro-2-furfuryl group in this compound with the 4-pyridyl group caused a decrease in activity, as indicated by the higher MIC value (6.25 mcg./ml.) for Compound 28. However, replacing the 5-nitro-2-furfuryl group with the 3-pyridyl group destroyed or greatly reduced the activity against *B. subtilis*.

3. When the aldehyde moiety in the hydrazone structures was identical, the 1-benzhydrylpiperazine derivatives appeared to give the best activity. For example, Compound 27 was more active than Compounds 6 and 15 against *B. subtilis*. Although both Compounds 6 and 27 had the same MIC value (15 mcg./ml.) against *Cl. perfringens*, Compound 27 caused partial inhibition of bacterial growth at a concentration of 1.9 mcg./ml. Again, Compound 28 was more active against *S. aureus* and *B. subtilis* than the corresponding Compounds 7 and 18.

4. The presence of a nitro group seemed to have a favorable effect on the antimicrobial activity of the compounds. Four of the seven active hydrazones contained a nitro group in the molecule. Perhaps the best illustration was that while Compound 12 did not show any activity against *S. aureus* at a concentration of 30 mcg./ml., Compound 15 did inhibit bacterial growth at a concentration as low as 3.13 mcg./ml.

5. Prescott *et al.* (4) reported that 1,4-bis(2-hydroxybenzylideneamino)piperazine, 1,4-bis(5-nitro-2-hydroxybenzylideneamino)-piperazine, and 1,4-bis(3,4-dichlorobenzylideneamino)piperazine could completely suppress the growth of *S. aureus* at a concentration of 4 mcg./ml. With the exception of Compound 15, the corresponding hydrazones of 1-phenyl-, 1-benzyl-, and 1-benzhydryl-4-aminopiperazines were not growth inhibitors of *S. aureus*. Even Compound 15 was about six times less active than 1,4-bis(5-nitro-2-hydroxybenzylideneamino)piperazine. On the basis of these observations, it would appear that in this type of compound the antibacterial activity against *S. aureus* was a function of the hydrazone moiety, although the piperazine nucleus might have had some favorable influence.

REFERENCES

(1) M. Nakanishi and T. Muro, Japanese pat. 68 13,467; through *Chem. Abstr.*, **70,** 11719n(1969).

(2) A. Pedrazzoli and L. Dall'Asta, French pat. 1,548,391; through *Chem. Abstr.*, **71,** 112982u(1969).

(3). P. Kozhukharov and T. Kharizanova, *Tr. Nauchnoizsled. Khim-Farm. Inst.*, **5,** 118(1966); through *Chem. Abstr.*, **68,** 1829t (1968).

(4) B. Prescott, G. Lones, and G. Caldes, *Int. J. Clin. Pharmacol.*, **1,** 529(1968).

(5) P. M. Kochergin and G. A. Karpov, *Khim. Farm. Zh.*, **1967,** 9; through *Pharm. Chem. J.*, **1967,** 8.

(6) L. J. Kitchen and C. B. Pollard, *J. Org. Chem.*, **8,** 338(1943).

(7) R. N. Prasad, L. R. Hawkins, and K. Tietje, *J. Med. Chem.*, **11,** 1144(1968).

(8) E. A. Conroy, U. S. pat. 2,663,706; through *Chem. Abstr.*, **49,** 4730g(1955).

(9) J. E. Cusic and P. Yonan, U. S. pat. 3,265,687; through *Chem. Abstr.*, **65,** 13764d(1966).

(10) J. W. Cusic and E. F. LeVon, U. S. pat. 3,183,229; through *Chem. Abstr.*, **63,** 16366g(1965).

(11) L. W. Morgan, D. H. Cronk, and R. P. Knott, *J. Pharm. Sci.*, **58,** 942(1969).

(12) J. W. Baker, G. L. Bachman, I. Schumacher, D. P. Roman, and A. L. Tharp, *J. Med. Chem.*, **10,** 93(1967).

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